REMARKS

The First Rejection Under 35 USC § 112, first paragraph

The Office Action alleges that the disclosure does not provide enablement for compounds in which radicals R^1, R^2, R^4, $R^{4'}$, R^5 and $R^{5'}$ exhibit 5 to 10-membered heteroaryl rings with 1 to 4 hetero atoms selected from N, S and O while citing several of the factors from *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). In this respect the rejection presents no rational as to why these claims are not enabled, but merely states conclusions. Specifically, it alleged that the application is not enabled, the claims are broader than the scope of enablement, and the specification lacks sufficient direction and guidance. These are mere conclusions. The rejection fails to set forth any rationale or evidence as to how the Examiner arrived at a conclusion of non-enablement.

However, even before one gets to the *Wands* factors, the courts have placed the burden upon the PTO to provide evidence shedding doubt on the disclosure that the invention can be made and used as stated. The disclosure "*must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statement contained therein, which must be relied on for enabling support." See *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). No such evidence or reason for doubting Applicants' disclosure is provided.

Doubt has been held reasonable where, for example, the invention has been characterized as "highly unusual," *In re Houghton*, 433 F.2d 820 (CCPA 1970), as "incredible," *In re Citron*, 325 F.2d 248, (CCPA 1963), or as "too speculative," *In re Eltgroth*, 419 F.2d 918 (CCPA 1970). The preparation of compounds having a variety of heterocyclic groups is not objectively doubtable, i.e., not "highly unusual," "incredible," and/or "too speculative." Thus, the rejection should be withdrawn for this reason alone.

Nevertheless, applicants address the *Wands* factors recited by the Office Action.

The court in *Wands* held that the test for enablement is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

The court in *In re Angstadt*, 10 USPQ 214, 219 (CCPA 1979), where the court

acknowledged the art involved, i.e., catalysis, to be unpredictable, also said that the test for enablement is not whether any experimentation is needed, but whether or not that experimentation is undue. In addition, even a considerable amount of experimentation or complex experimentation is permissible if it is routine. See, e.g., *Ex parte Jackson*, 217 USPQ 804, 807 (POBA 1982).

The specification provides ample guidance on how the claimed compounds are prepared, i.e., both broad teachings as well as specific reaction schemes to achieve the claimed compound, as well as specific examples are provided, in addition to pointing to references that teach the preparation of the claimed compounds. The specification, for example, provides exemplary hereroaryls on page 10, second full paragraph. The specification teaches that

> "production of the compounds according to the invention is carried out analogously to known processes that are described in, for example, EP 531 883. If the production of the starting compounds is not described, the starting compounds are known and are commercially available or their production is carried out analogously to the processes described here."

See page 43 of the specification. EP '883 teaches the preparation of compounds containing heterocyclic groups.

Following the quoted statement, the disclosure on pages 44-53 sets forth eighteen different general operating instructions for use in preparing the compounds of the claimed genus containing N, S and O atoms. Thereafter, from page 54 to page 199, Applicants' present no less than 306 synthesis examples demonstrating how to prepare compounds in accordance with the claimed genus. These synthesis examples include compounds which exhibit heterocyclic groups. For example, pyridinyl, pyridyl, thienyl, imidazol, indonyl, furyl, pyrrolidin, morpholin, piperidin, and piperazine are exemplified heterocyclic groups in compound according to the invention. (New claims 41 and 42 define the heterocycles as the exemplified groups.) These groups are representative of the claimed genus and compounds containing them are actually synthesized, i.e., are thus clearly enabled. No rationale or evidence was provided by the Patent Office as to why one of ordinary skill in the art based on this vast amount of disclosure and guidance would be unable to prepare without undue experimentation the claimed compounds.

Additionally, "the [enablement] requirement is satisfied if, given what they [those of

ordinary skill in the art] already know, the specification teaches those in the art enough that they can make and use the invention without 'undue experimentation.'" See *Amgen v Hoechst Marion Roussel*, 65 USPQ2d 1385 (CA FC 2003). Making the compounds of the claimed invention would be routine for those of ordinary skill in the art since they are prepared analogously to known processes. See, for example, *Spectra-Physics v Coherent*, 827 F.2d 1524, 3 USPQ2d 1737 (Fed. Cir. 1987) ("A patent need not teach, and preferably omits, what is well known in the art"); *In re Howarth,* 654 F.2d at 105, 210 USPQ 689 (CCPA 1981) ("An inventor need not ... explain every detail since he is speaking to those skilled in the art."); *In re Gay*, 309 F.2d 769, 774, 135 USPQ 311 (CCPA 1962) ("Not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be.")

Explicitly providing examples for preparing species having each possible heterocyclic group is not necessary to enable the full scope of the claims. There is no such requirement imposed by law. See, for example, *In re Angstadt*, 537 F.2d at 502-03, 190 USPQ 214 (CCPA 1976) (deciding that applicants "are *not* required to disclose *every* species encompassed by their claims even in an unpredictable art"); *Utter v Higara*, 845 F.2d at 998-99, 6 USPQ2d 1714 (CAFC 1988) (holding that a specification may, within the meaning of Section 112, Para. 1, enable a broadly claimed invention without describing all species that claim encompasses).

Instead, there is no requirement for <u>any</u> examples. See, for example, *Marzocchi*, supra, stating that "an enabling teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance." The MPEP also states that "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." See MPEP § 2164.02.

The PTO has failed to meet its burden of establishing that the disclosure does not enable one skilled in the art to make the compounds recited in the claims. Instead of relying on proper probative evidence, the rejection is improperly based on the bare allegation that the disclosure does not provide enablement to all of the claimed rings. No evidence has been presented which would demonstrate that the guidance provided by the specification or what is already known in the art is inadequate to enable the preparation of the claimed compounds without undue experimentation. In light of the disclosure, taken in combination with knowledge possessed by one of ordinary skill in the art, sufficient guidance is provided to objectively enable one of ordinary skill in the art to make and use the claimed invention, including those compounds exhibiting heterocyclic groups, using no more than routine

experimentation.

Claims 28 and 30

Separate consideration of claims 28 and 30 is requested as they recite a narrower scope for the heterocyclic groups than in the independent claims. The heterocyclic rings in these claims consist of a group of specific heterocycles that are identified by name.

Claims 39 and 40

Separate consideration for these two new independent claims is requested. The substituents on the compound of formula I are defined to contain no heterocyclic groups.

Claims 41 and 42

Separate consideration is also requested for claims 28 and 30 as the heterocyclic groups are defined as a specifically named Markush group of heterocyclic groups that were exemplified in the examples of the specification.

Claims to Specific Compounds

Claims 11 and 12 are drawn to specifically named compounds. Their preparation is exemplified in the specification. There is absolutely no basis for rejecting these claims for lack of enablement.

The Second Rejection Under 35 USC § 112, first paragraph

Even though applicants disagree with the rejections for reasons of record, to further the prosecution of this application, applicants have amended the claims directed to methods of uses to specifically named diseases.

The amendments overcome the rejections.

Claim 15 is now directed to chronic inflammation. This practical utility is taught on page 1 of the specification.

Dependent claim 33 is directed to neuroinflammation and new dependent claim 37 is directed to neuronal dysfunction and degeneration. The specification on page 1 teaches that

> Almost all degenerative diseases of the central nervous system are connected to chronic inflammation. A central step of the inflammation process is the activation of mononuclear phagocyte cells, the microglia. This is carried out in, e.g., Alzheimer's disease by senile plaques, in Creutzfeldt-

Jacob disease by a prion protein and in ischemic stroke by dead cells. The microglia can remain for a prolonged period in the activated state, in which they produce and secrete various inflammation factors, e.g., reactive oxygen/nitrogen intermediate products, proteases, cytokines, complement factors and neurotoxins.

The latter in turn produce neuronal dysfunction and degeneration. (emphasis added)

Dependent claim 34 is directed to stroke and new dependent claim 38 is directed to Alzheimer's disease. The specification on page 40-41 teaches that

Example 307 describes how the inhibition of the microglia activation can be measured. In this case, the activation of the microglia can be carried out by various stimuli, such as, e.g., Aβ-peptide (β-amyloid, Araujo, D. M. and Cotman, C. M. Brain Res. 569, 141-145 (1992)), prion protein, cytokines or by cell fragments (Combs, C. K. et al. (1999) J. Neurosci., 19, 928-939, Wood, P. L. (1998) Neuroinflammation: Mechanisms and Management, Humana Press). For example, the compound of Example 49, 6-[[1-(4-methylphenyl)-2-phenyl-1H-benzimidazol-6-yl]oxy]hexanoic acid isopropyl ester indicates an inhibition of IC_{50} = 0.75 μm.

The stimulation with the Aβ-peptide corresponds to the pathophysiological situation in Alzheimer's disease. In this test, the substances according to the invention showed inhibition of microglia activation in the case of stimulation with the Aβ-peptide. The inhibition of the microglia activation by the substances according to the invention results in a strong reduction of the cytokine production and secretion, e.g., of Il1β and TNFα (measured by ELISA and mRNA expression analysis) and in a reduced secretion of reactive oxygen/nitrogen intermediate products. Several inflammation factors are thus equally inhibited.

The in vivo action of the substances according to the invention was shown in an MCAO model in rats [see example 308]. This model simulates the state of a stroke. The substances according to the invention reduce the microglia activation, which occurs in the case of active brain lesions in the brains of animals. (emphasis added)

Applicants submit that all the claimed utilities are practical utilities that are related and are enabled by the specification.

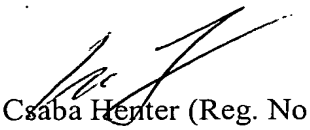
Rejections Under 35 USC § 112, second paragraph

The amendments to the claims overcome the rejections to the form of the claims and to use language in accordance with conventional U.S. practice. The claims are not narrowed.

Reconsideration of all the rejections is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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